

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : 10/560,337
Applicant : Valerio Cioli
Filed : December 9, 2005
Docket No. : BUG5-39170

DECLARATION OF BRUNO SILVESTRINI

Bruno Silvestrini declares as follows:

1. I presently reside at Via Michelangelo Schipa, 15 - I-00179 Rome, Italy.
2. I am the assignee, together with Michele Bonanomi, of the above-referenced U.S. Patent Application Serial No. 10/560,337 filed December 9, 2005.
3. My educational background is as follows. I received a Bachelor's Degree in Medicine and Surgery from the University of Bologna in 1955. From 1957 to 1959, I was director of the Neuropharmacology Laboratory of Lepetit in Milan (Italy); From 1959 to 1983 I was director of "Istituto di Ricerca F. Angelini", in Rome (Italy); From 1983 to 2004, I was professor at the University "La Sapienza" in Rome and director of the Pharmacology of Natural Substances and General Physiology departments. Since 1984 I have been the president of the Noopolls Foundation. During my professional activity I have discovered and patented the following active ingredients: oxalamine, benzidamine, proxazole, bendazac, trazodone, dapiprazole, lonidamine. I am the author of 478 scientific articles, 34 granted US patents and many other scientific publications and books.
4. With respect to the invention described in the above-referenced patent application, certain experiments were conducted under my supervision. These experiments demonstrate that rapid onset of the therapeutic effect of the present formulation can be obtained. The experiments are described as follows. Two sublingual formulations comprising 25 mg and 50 mg of nimesulide, respectively, and an oral tablet comprising 100 mg of nimesulide were administered to the same panel of 6 patients. The blood concentration of nimesulide was tested at fixed times, starting immediately after administration and up to 8 hours after the administration.
5. The enclosed graph (EXHIBIT A) shows that with the sublingual formulations of the invention the maximum blood concentration (i.e. the maximum effect) is achieved about half an

hour after administration and the effect goes to about zero after about two and a half hours. On the contrary, with the oral administration, the maximum therapeutic effect is achieved after about two hours from administration and remains constant for more than 8 hours.

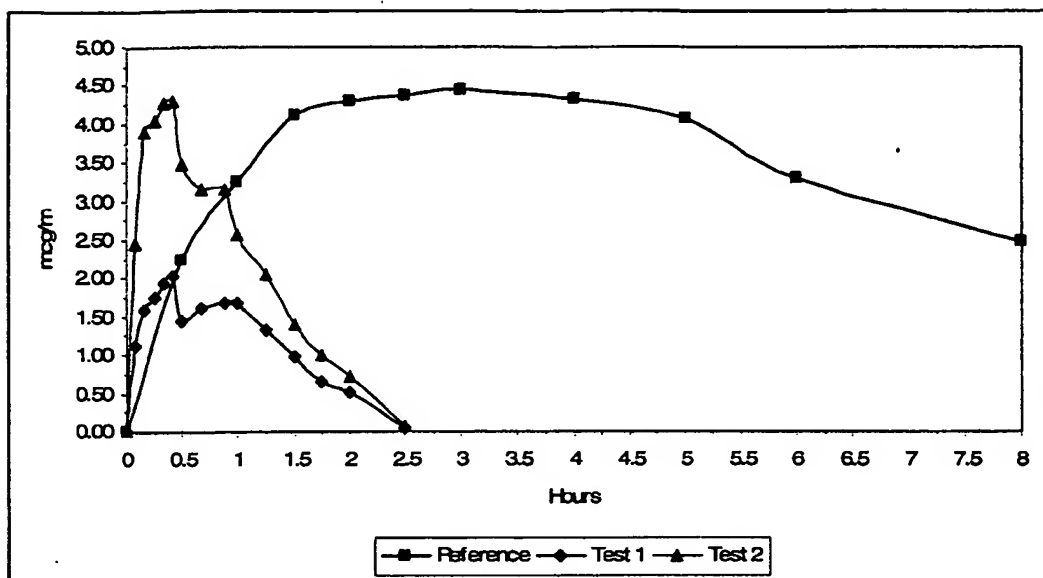
6. The above experiments demonstrate the rapid onset of the therapeutic effect of nimesulide and demonstrate that the sublingual formulation of the invention solves the problem of providing a drug formulation for the treatment of acute inflammatory diseases, i.e. pathologies that need a rapid onset of the therapeutic effect and low side effects. Based on the prior art, the results of the present invention are surprising and unexpected. The present inventor has unexpectedly and surprisingly found that the combination of the desired therapeutic effect and low side effects can be achieved by reducing the standard oral dosage of active principle. Moreover, the effect is achieved in a quicker manner than oral administration. Accordingly, the sublingual formulation of the invention is suitable to treat acute inflammatory conditions, which need a quick response and low side effects.

7. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the patent application or any patent issued thereon.

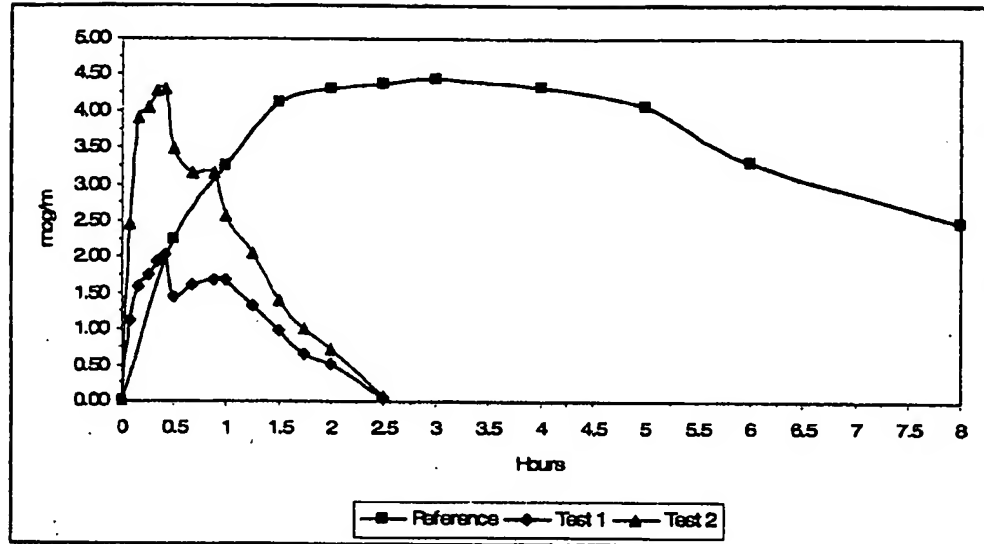
September 17, 2008

Date

Bruno Silvestrini
Bruno Silvestrini



Test 1 : Nimesulide 25 mg sublingual tablet
Test 2 : Nimesulide 50 mg sublingual tablet
Reference : commercial nimesulide, 100 mg oral tablet



Test 1 : Nimesulide 25 mg sublingual tablet
Test 2 : Nimesulide 50 mg sublingual tablet
Reference : commercial nimesulide, 100 mg oral tablet